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Predominant (*S*)-Enantioselective Inclusion of Aryl Methyl Sulfoxides by (*S*)-Isoleucyl-(*S*)-phenylglycines

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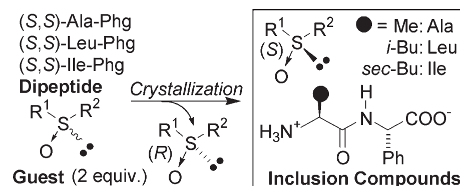

In terms of chiral recognition for *racemic* aryl methyl sulfoxides in the solid state, three kinds of crystalline (*S*)-alkylglycyl-(*S*)-phenylglycines were examined as potential dipeptides host molecules. When (*S*)-alanyl-(*S*)-phenylglycines [(*S*,*S*)-Ala-Phg] crystallized with aryl methyl sulfoxides, the stereochemistry of preferentially included sulfoxides depended on the individual shapes of the sulfoxides and the enantiomeric excess was relatively low. Although (*S*)-leucyl-(*S*)-phenylglycines [(*S*,*S*)-Leu-Phg] and (*S*)-isoleucyl-(*S*)-phenylglycines [(*S*,*S*)-Ile-Phg] mainly included the *S*-form of aryl methyl sulfoxides, the enantiomeric recognition of (*S*,*S*)-Ile-Phg was superior to that of (*S*,*S*)-Leu-Phg. Single-crystal X-ray analysis of these inclusion compounds revealed that the dipeptide molecules self-assembled to form layer structures and included sulfoxides between these layers through hydrogen bonding between the proton of $^{+}NH_3$ and the oxygen of the sulfoxide. Besides these host−guest interactions, the phenyl groups of the sulfoxides interacted with each other through the phenyl−phenyl interaction. Two adjacent homochiral sulfoxides make a pair having a 2-fold screw axis along the channel cavity. Thus, the self-recognition of sulfoxides made 2_1 helical column structures and had high enantioselectivity.

Introduction

Chiral sulfoxides are now widely used not only as important auxiliaries to bring about numerous asymmetric synthesis but also as biologically significant molecules.[1] Many methods are presently available to obtain optically active sulfoxides: asymmetric oxidation, optical resolution, and nucleophilic addition of alkyl or aryl ligands to diastereochemically pure chiral sulfinates, the so-called Andersen procedure.[2] However, the Andersen method requires the separation of the diastereomeric sulfinates except for commercially available chiral sulfinates, such as (*S*)-menthyl *p*-toluenesulfinates. For the preparation of chiral sulfoxides, asymmetric oxidation is undoubtedly beneficial in the case of high enantioselectivity. If the enantioselectivity of the sulfide oxidation is quite low, optical resolution of the racemic sulfoxides must be an alternative approach. Generally, acidic or basic compounds are optically resolved by forming diastereomeric salts with appropriate chiral resolving agents, but the method is not acceptable for neutral sulfoxides. Recently, the optical resolution of neutral compounds by lattice inclusion compounds, namely, clathrates, attracts significant attention on account of its high efficiency and simplicity.[3] Some sulfoxides were optically resolved by dipeptides[4] as well as several artificial host molecules.[5]

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(3) *Separations and Reactions in Organic Supramolecular Chemistry*; Perspectives in Supramolecular Chemistry; Toda, F., Bishop, R., Eds.; John Wiley & Sons: West Sussex U.K., 2004; Vol. 8.

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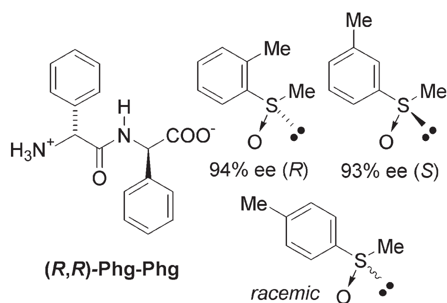


FIGURE 1. Structure of (*R*)-phenylglycyl-(*R*)-phenylglycine [(*R*,*R*)-Phg-Phg] and the stereochemistry of methyl tolyl sulfoxides included in the cavity of (*R*,*R*)-Phg-Phg.

In this context, we demonstrated high enantioselective inclusion of aryl methyl sulfoxides using (*R*)-phenylglycyl-(*R*)-phenylglycine [(*R*,*R*)-Phg-Phg].[4d−f] The host molecules self-assemble by intermolecular salt formation to form layer structures, and the sulfoxide guests are accommodated between layers. Although the enaitoselectivity is high, we face a crucial problem that the stereochemistry of preferably included sulfoxides is dependent on the shape of aryl methyl sulfoxides. For the isomers of methyl tolyl sulfoxide, the enantioselectivities were as follows: 2-tolyl, 94% ee (*R*); 3-tolyl, 93% ee (*S*); 4-tolyl, racemic (Figure 1).[4d] Similar enantioselectivities were obtained for isomers of chlorophenyl methyl sulfoxide.

In addition, we elucidated that a slight difference in the shape of the guest molecule induces a conformational change in (*R*,*R*)-Phg-Phg, especially the phenyl group of the dipeptides. As can be seen from the crystal structure of (*R*,*R*)-Phg-Phg with (*R*)-chlorophenyl methyl sulfoxide (Figure 2), the phenyl−phenyl interaction between host and guest occurs most frequently. Since the phenyl−phenyl interaction controls the position of sulfoxides in the cavity of (*R*,*R*)-Phg-Phg, it is difficult for us to predict whether the *R*- or *S*-form of the sulfoxide is predominantly included.

To overcome the problem, the phenyl group of the *N*-terminal amino acid was replaced by three alkyl groups. It is just like enzyme proteins choose appropriate amino acids to construct the specific recognition site. We try to examine three kinds of (*S*)-alkylglycyl-(*S*)-phenylglycines, (*S*)-alanyl-(*S*)-phenylglycines [(*S*,*S*)-Ala-Phg], (*S*)-leucyl-(*S*)-phenylglycines [(*S*,*S*)-Leu-Phg], and (*S*)-isoleucyl-(*S*)-phenylglycines [(*S*,*S*)-Ile-Phg] (Scheme 1).

In the course of the study, we found that (*S*)-alkylglycyl-(*S*)-phenylglycines form inclusion compounds with aryl methyl sulfoxides, where the homochiral guest molecules aggregate 2_1 helical columns by the phenyl−phenyl interaction to achieve high enantioselectivity. It is noteworthy that (*S*)-form of all

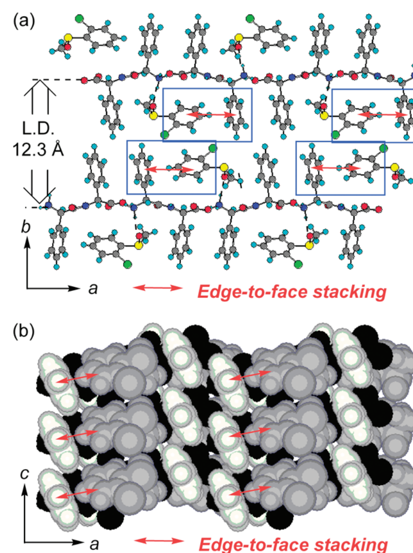
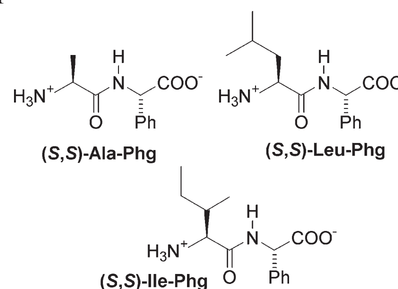
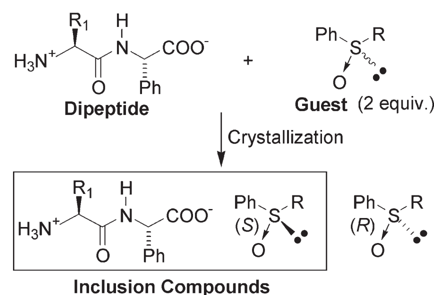


FIGURE 2. Inclusion compound of (*R*,*R*)-Phg-Phg·(*R*)-2-chloromethyl phenyl sulfoxide. (a) Layer structure. (b) CPK model of packing where sheet structures are colored in black, guest sulfoxides in gray, and phenyl groups of dipeptides in white.

SCHEME 1



SCHEME 2



aryl methyl sulfoxides that have phenyl, tolyl, and xylyl groups are included in (*S*)-isoleucyl-(*S*)-phenylglycine. These interactions between guest molecules in the cavity of (*S*)-alkylglycyl-(*S*)-phenylglycines were different from what was observed in the case of (*R*,*R*)-Phg-Phg. In other words, the present work provided us a greater understanding of the role of side chains of the *N*-terminal amino acid for chiral discrimination of aryl methyl sulfoxides.

Results and Discussion

Enantioselective Inclusion of Alkyl Phenyl Sulfoxides. (*S*,*S*)-Ala-Phg, (*S*,*S*)-Leu-Phg, and (*S*,*S*)-Ile-Phg were easily prepared in accordance with the synthetic method of

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TABLE 1. Enantioselective Inclusion of Alkyl Phenyl Sulfoxides by Dipeptides

	guest RSOPh		(*S*,*S*)-Ala-Phg			(*S*,*S*)-Leu-Phg			(*S*,*S*)-Ile-Phg		
entry	R		ee (%)	G/H[a] ratio	LD[b] (Å)	ee (%)	G/H[a] ratio	LD[b] (Å)	ee (%)	G/H[a] ratio	LD[b] (Å)
1	Me	**1**	*rac*[c]	1.00	11.5	73(*S*)	0.97	11.7	80(*S*)	0.97	11.1
2	Et	**2a**	*rac*[c]	0.87	11.8	33(*S*)	0.63	12.7	17(*S*)	0.57	12.6
3	*i*-Pr	**3a**	15(*S*)	0.63	12.3	15(*S*)	0.51	12.5	*rac*[c]	0.67	12.7
4	*n*-Pr	**3b**	*rac*[c]	0.90	11.5	*rac*[c]	0.54	11.7		0.09	12.4

[a]G/H ratio means the ratio of the sulfoxide (guest) to the dipeptide (host) in the inclusion compound. [b]LD is an interlayer distance measured by PXRD. [c]*rac* means enantioselectivity within 10%.

(*R*,*R*)-Phg-Phg,[5] and their inclusion abilities were examined. The inclusion compound was prepared by crystallization of the dipeptide in the presence of a *racemic* sulfoxide (Scheme 2).

Table 1 summarizes the results for the inclusion of alkyl phenyl sulfoxides with (*S*,*S*)-Ala-Phg, (*S*,*S*)-Leu-Phg, or (*S*,*S*)-Ile-Phg. Here, G/H ratio means the ratio of the sulfoxide (guest) to the dipeptide (host). After dissolving the inclusion compound with appropriate deuterated solvents, the ratios were determined by ^{1}H NMR measurement. The layer distances (LD in Tables) were determined by powder X-ray diffraction (PXRD). All of these inclusion compounds have strong diffraction peaks in the lower 2Θ range. The layer distances were assigned by the strong peak of PXRD, which corresponds to the diffraction plane of the peptide backbones in the single crystal structure (vide infra). (*S*,*S*)-Ala-Phg showed inclusion ability but less enantioselectivity for these sulfoxides. (*S*,*S*)-Leu-Phg and (*S*,*S*)-Ile-Phg showed a similar tendency in molecular recognition. Among these alkyl phenyl sulfoxides, only methyl phenyl sulfoxide was included in both (*S*,*S*)-Leu-Phg and (*S*,*S*)-Ile-Phg with high enantioselectivity (entry 1).

Pairing of the Guests in the Chiral Cavities. The crystal structure of the inclusion compound of (*S*,*S*)-Ile-Phg with methyl phenyl sulfoxide was determined by performing single-crystal X-ray diffraction analysis (Figure 3, space group $P2_12_12_1$). In the inclusion crystals, the dipeptide molecules have a straight glycylglycine backbone forming a two-dimensional layer by means of intermolecular salt formation and hydrogen bonding between COO^- and $^+NH_3$ groups.[3] The sheet structure of (*S*,*S*)-Ile-Phg was similar to that of (*R*,*R*)-Phg-Phg. Methyl phenyl sulfoxide was accommodated in the channel between *sec*-butyl and phenyl groups of the dipeptides. As mentioned above, the *N*-terminal phenyl group of (*R*,*R*)-Phg-Phg interacted with the phenyl group of (*R*)-2-chlorophenyl methyl sulfoxide (see in Figure 2). However, the methyl phenyl sulfoxide in (*S*,*S*)-Ile-Phg did not contact with the phenyl groups of (*S*,*S*)-Ile-Phg but did interact with the phenyl group of the adjacent sulfoxide belonging to the upper layer. These phenyl−phenyl interactions contribute to the secondary structure in proteins[6] as well as to artificial supramolecular aggregate.[7]

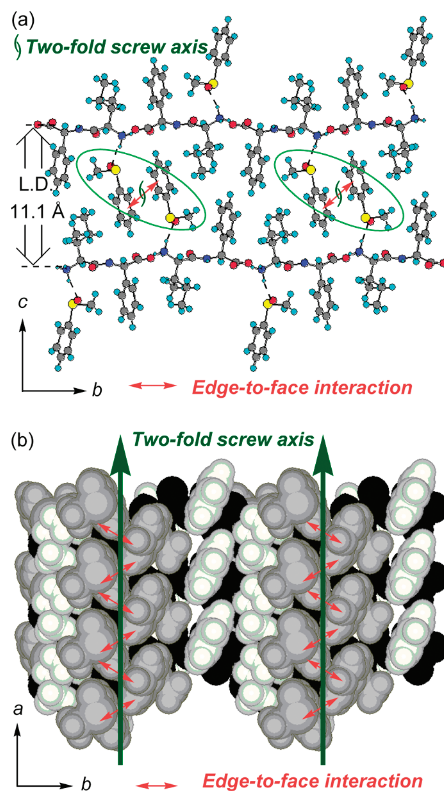

FIGURE 3. Inclusion compound of (*S*,*S*)-Ile-Phg·(*S*)-methyl phenyl sulfoxide **1**. (a) Layer structure. (b) CPK model of packing where sheet structures are colored in black, guest sulfoxides in gray, and phenyl groups of dipeptides in white.

The above results indicate that methyl phenyl sulfoxide paired in the channel cavity to form symmetrical columns with a 2-fold screw axis. In other words, this pairing of sulfoxides with the same chirality involved the self-recognition process of the guest. Highly enantioselective inclusion occurred and thereby aided pairing of the guests in the host cavity.

Enantioselective Inclusion of Methyl Phenyl Sulfoxides. Next, we investigated how the methyl substituent group on the phenyl group of sulfoxides influences the stereoselective inclusion. Table 2 summarizes the results for enantioselective inclusion of the dipeptides [(*S*,*S*)-Ala-Phg, (*S*,*S*)-Leu-Phg, and (*S*,*S*)-Ile-Phg] for both structural isomers of methyl tolyl sulfoxides (**2b**−**2d**) and methyl xylyl sulfoxides (**3c**−**3h**).

Although (*S*,*S*)-Ala-Phg included these sulfoxides, the enantioselectivity was low except for methyl 3,5-xylyl sulfoxide **3g** (65% ee) and methyl 3,4-xylyl sulfoxide **3h** (75% ee) (entries 8 and 9). The absolute configuration of preferably included sulfoxides depended on the individual shape of the

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TABLE 2. Enantioselective Inclusion of Structural Isomers by Dipeptides

	guest ArSOMe		(*S*,*S*)-Ala-Phg			(*S*,*S*)-Leu-Phg			(*S*,*S*)-Ile-Phg		
entry	Ar		ee (%)	G/H[a] ratio	LD[b] (Å)	ee (%)	G/H[a] ratio	LD[b] (Å)	ee (%)	G/H[a] ratio	LD[b] (Å)
1	2-MeC_6H_4	**2b**	11(*R*)	0.64	11.8	*rac*[c]	0.57	11.7	83(*S*)	0.99	14.7
2	3-MeC_6H_4	**2c**	*rac*[c]	0.73	11.4	13(*S*)	0.67	11.7	41(*S*)	0.98	14.9
3	4-MeC_6H_4	**2d**	40(*R*)	0.95	12.5	49(*S*)	0.51	12.8	79(*S*)	0.97	12.0
4	2,6-$Me_2C_6H_3$	**3c**	28(*R*)	0.56	12.9	52(*S*)	0.89	11.4	83(*S*)	0.91	12.5
5	2,3-$Me_2C_6H_3$	**3d**	46(*R*)	0.51	13.2	*rac*[c]	0.63	11.7	93(*S*)	1.00	14.2
6	2,5-$Me_2C_6H_3$	**3e**	16(*R*)	0.55	12.3	*rac*[c]	0.52	11.8	72(*S*)	0.90	14.1
7	2,4-$Me_2C_6H_3$	**3f**	22(*R*)	0.76	13.0	*rac*[c]	0.68	12.4	91(*S*)	0.90	12.3
8	3,5-$Me_2C_6H_3$	**3g**	65(*S*)	0.95	12.4	53(S)	0.59	11.7	84(*S*)	0.43	11.4
9	3,4-$Me_2C_6H_3$	**3h**	75(*S*)	0.55	12.3	77(*S*)	0.99	12.1	79(*S*)	0.96	12.0

[a]G/H ratio means the ratio of the sulfoxide (guest) to the dipeptide (host) in the inclusion compound. [b]LD is the interlayer distance measured by PXRD. [c]*rac* means enantioselectivity within 10%.

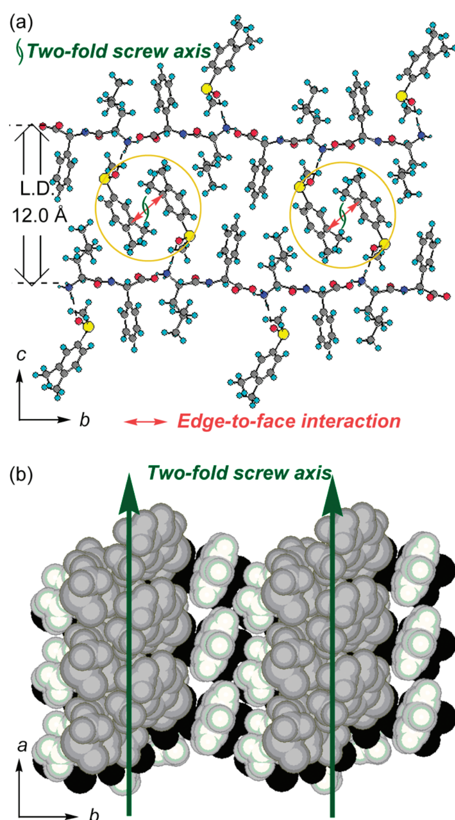


FIGURE 4. Inclusion compound of (*S*,*S*)-Leu-Phg·(*S*)-methyl 3,4-xylyl sulfoxide **3h**. (a) Layer structure. (b) CPK model of packing where sheet structures are colored in black, guest sulfoxides in gray, and phenyl groups of dipeptides in white.

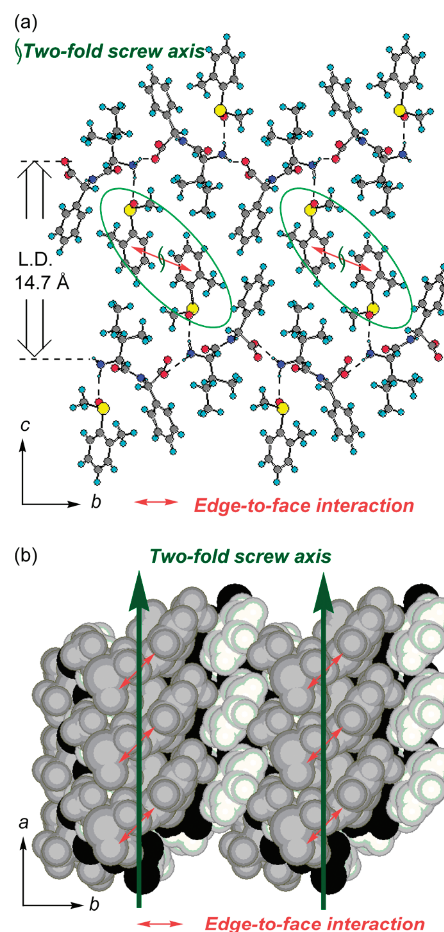
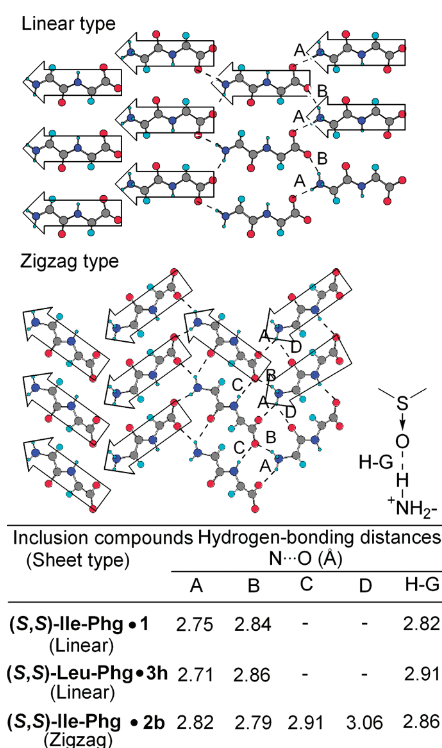


FIGURE 5. Inclusion compound of (*S*,*S*)-Ile-Phg·(*S*)-methyl 2-tolyl sulfoxide **2b**. (a) Layer structure. (b) CPK model of packing where sheet structures are colored in black, guest sulfoxides in gray, and phenyl groups of dipeptides in white.

guest. Since alanine has only a methyl group as the side chain, the cavity might not be enough for chiral discrimination of the sulfoxide. In the case of (*S*,*S*)-Leu-Phg, the sulfoxides having the phenyl group with an *o*-methyl group were included with no enantioselectivity (entries 1 and 5−7). (*S*,*S*)-Leu-Phg included the (*S*)-form of other sulfoxides without an *o*-methyl group, but the enantiomeric excess was not enough (entries 2−4, and 8). Only methyl 3,4-xylyl sulfoxide **3h** was included in (*S*,*S*)-Leu-Phg with high enantiomeric excess (77% ee), and the inclusion compound could be analyzed in single-crystal X-ray analysis (vide infra).

In sharp contrast with (*S*,*S*)-Leu-Phg, (*S*,*S*)-Ile-Phg generally included both methyl tolyl sulfoxides and methyl xylyl sulfoxides with high (*S*)- enantioselectivity, even though the sulfoxides had a methyl group at the *ortho* position of the phenyl group. Table 2 indicates that these layer distances of (*S*,*S*)-Ile-Phg are often over 14 Å and generally longer than that of (*S*,*S*)-Leu-Phg.

Crystal Structures of Inclusion Compounds. Among the sulfoxides listed in Table 2, (S,S)-Leu-Phg with methyl 3,4-xylyl sulfoxide **3h** and (*S*,*S*)-Ile-Phg with methyl 2-tolyl sulfoxide **2b** were single crystals suitable for X-ray analysis (Figures 4 and 5). The space group of these crystals was $P2_12_12_1$. The figures clearly show the pairing of sulfoxide



Inclusion compounds (Sheet type)	Hydrogen-bonding distances N···O (Å)				
	A	B	C	D	H-G
(*S*,*S*)-Ile-Phg • 1 (Linear)	2.75	2.84	-	-	2.82
(*S*,*S*)-Leu-Phg • 3h (Linear)	2.71	2.86	-	-	2.91
(*S*,*S*)-Ile-Phg • 2b (Zigzag)	2.82	2.79	2.91	3.06	2.86

FIGURE 6. Sheet structures of dipeptide backbones and hydrogen-bond distances in these inclusion compounds.

guests in the cavity of these inclusion crystals. Figure 4 shows that methyl 3,4-xylyl sulfoxide **3h** got together through an edge-to-face interaction to form a 2_1 symmetrical guest column along the channel cavity,

The inclusion compound of (*S*,*S*)-Ile-Phg with (*S*)-methyl 2-tolyl sulfoxide **2b** has a pleated sheet, whose interlayer distance was 14.7 Å (Figure 5). The pleated sheet is why the layer distances of (*S*,*S*)-Ile-Phg are longer than those of (*S*,*S*)-Leu-Phg. The figures clearly show the pairing of guests in the cavity and the forming a 2_1 screw symmetrical column through the edge-to-face interaction along the channel cavity of these inclusion crystals. Furthermore, isoleucine (Ile) involves an additional chirality on the *sec*-butyl group (*S*-configuration). The chiral side chain acts as the wall of the narrow cavity so as to enrich the chiral circumstance for enatioselective recognition, even though the sulfoxides have an *o*-methyl group on the phenyl group.

Figure 6 shows the sheet structures of the dipeptide backbones and hydrogen-bonding distances in these inclusion compounds. In two of the three inclusion crystals mentioned above, the conformation of the dipeptide backbones is very similar for forming the sheet structure from the hydrogen-bonding network. The lengths of the hydrogen bonds between COO^- and $^+NH_3$ groups are almost the same as the reported distances for (*R*,*R*)-Phg-Phg with (*R*)-2-chlorophenyl methyl sulfoxide in Figure 2.[5a] However, the inclusion compound of (*S*,*S*)-Ile-Phg with (*S*)-methyl 2-tolyl sulfoxide has a dipeptide backbone with a zigzag arrangement and another two hydrogen bonds. One hydrogen bond is an additional linkage (bond C) between COO^- and a hydrogen atom of the amide group. The other bond (bond D) is between $^+NH_3$ and an oxygen atom of the amide group. It is these hydrogen bonds that are responsible for the zigzag alignment of the dipeptide backbones. Like the hydrogen bonds between the dipeptide hosts, the hydrogen-bonding distances (H···G) between the $^+NH_3$ group and the sulfinyl oxygen are close to one another.

Conclusions

Three dipeptides [(*S*,*S*)-Ala-Phg, (*S*,*S*)-Leu-Phg, and (*S*,*S*)-Ile-Phg] were prepared as a new series of (*S*)-alkylglycyl-(*S*)-phenylglycines, and they were examined in terms of enantiomeric recognition of sulfoxides. Although (*S*,*S*)-Ala-Phg included sulfoxides, its enantioselectivity was low and the stereochemistry of the preferably included sulfoxides depended on their shape. (*S*,*S*)-Leu-Phg and (*S*,*S*)-Ile-Phg included methyl phenyl sulfoxides. (*S*,*S*)-Ile-Phg showed high enantiselectivity for the (*S*)-form of sulfoxides. The dipeptide molecules self-assembled to form layer structures and included the sulfoxides between these layers. In particular, guest molecules with the same chirality aggregate 2_1 screw symmetric columns and have high enantioselectivity.

Experimental Section

Synthesis of (*S*)-Alkylglycyl-(*S*)-phenylglycine. The general preparation method of (*R*)-phenylglycyl-(*R*)-phenylglycine[8] was applied for (*S*)-alkylglycyl-(*S*)-phenylglycine. (S)-Alkylglycine and (*S*)-phenylglycine were protected with CbzCl (benzyloxycarbonyl chloride) and benzyl alcohol, respectively.[9,10] These protected amino acids were coupled with DCC (*N*,*N*′-dicyclohexylcarbodiimide) and HOBt (1-hydroxybenzotriazole) to form the corresponding protected dipeptide.[11] Final deprotection was performed by hydrogenation with Pd black under a hydrogen atmosphere to obtain (*S*)-alkylglycyl-(*S*)-phenylglycine. All steps proceeded in excellent yields.

(*S*,*S*)-Ala-Phg. Colorless crystals; mp 194.1 °C; $[\alpha]^{25}_D$ = +146.1 (*c* 0.10, H_2O); ^1H NMR (300 MHz, CD_3OD) δ 7.47−7.44 (m, 2H), 7.31−7.22 (m, 3H), 5.26 (s, 1H), 3.99 (q, 1H, *J* = 7.0 Hz), 1.53 (d, 3H, *J* = 7.0 Hz); IR (KBr) 3334, 2976, 2127, 1655, 1527, 1392, 1356, 1196, 1157, 737, 700 cm^{-1}; powder X-ray diffraction (I/I_0) 12.0 (0.89), 8.0 (0.25), 7.0 (0.15), 6.0 (0.13), 5.1 (0.46), 4.8 (1.00), 4.2 (0.82), 3.7 (0.70), 3.2 Å (0.42). Anal. Calcd for $C_{11}H_{14}N_2O_3$: C, 59.45; H, 6.35; N, 12,61. Found: C, 59.36; H, 6.32; N, 12.51.

(*S*,*S*)-Leu-Phg. Colorless crystals; mp 144 °C; $[\alpha]^{25}_D$ = +136.3 (*c* 0.29, MeOH); ^1H NMR (300 MHz, CD_3OD) δ 7.48−7.45 (m, 2H), 7.32−7.22 (m, 3H), 5.27 (s, 1H), 3.97 (m, 1H), 1.82−1.65 (m, 3H), 1.00 (t, 6H *J* = 6.4 Hz); IR (KBr) 3379, 3313, 2962, 1670, 1577, 1506,1375, 1232, 1074, 729, 696 cm^{-1}; powder X-ray diffraction (I/I_0) 11.7 (1.51), 8.1 (0.64), 7.2 (0.3 3), 5.0 (1.00), 4.4 (1.00), 4.0 (0.92), 3.8 Å (0.55). Anal. Calcd for $C_{14}H_{20}N_2O_3$: C, 63.62; H, 7.63; N, 10.60. Found: C, 63.27; H, 7.51; N, 10.23.

(*S*,*S*)-Ile-Phg. Colorless crystals; mp 171.0 °C; $[\alpha]^{25}_D$ = +139.1 (*c* 0.10, MeOH); ^1H NMR (300 MHz, CD_3OD) δ 7.48−7.45 (m, 2H), 7.28−7.22 (m, 3H), 5.27 (s, 1H), 3.83 (d, 1H, *J* = 5.6 Hz), 1.94−1.89 (m, 1H), 1.66−1.57 (m, 1H) 1.30−1.20 (m, 1H), 1.04 (d, 3H, *J* = 6.7 Hz); 0.98 (t, 3H, *J* = 6.7 Hz); IR (KBr) 3373, 3240, 2970, 2696, 2586, 2044, 1666, 1606, 1514, 1381, 733 cm^{-1}; powder X-ray diffraction (I/I_0) 11.6 (0.27), 9.2 (0.12), 7.5 (0.52), 5.4 (1.00), 4.6 (0.33), 4.4 (0.29), 3.9

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(0.36), 3.7 (0.32), 3.0 (0.55), 3.0 (0.23), 2.9 Å (0.29). Anal. Calcd for $C_{14}H_{20}N_2O_3 \cdot 0.67H_2O$: C, 60.84; H, 7.78; N, 10.14. Found: C, 60.83; H, 7.71; N, 10.06.

Synthesis of Sulfoxide 1, 2, and 3. Sulfides were prepared from corresponding halides and thiols by Williamson-typed sulfide synthesis except for methyl 2,3-xylyl sulfoxide **3d**.[12] Oxidation of sulfide was proceeded by hydrogen peroxide in acetic acid or sodium metaperiodate.[13] Except for phenyl propyl sulfoxide **3b**[14] and methyl 2,3-xylyl sulfoxide **3d**, all sulfoxides have already reported by our previous literature.[5a]

Preparation of Racemic Methyl 2,3-Xylyl Sulfoxide 3d. According the literature,[15] 2,3-xylyl Grignard reagent was reacted with dimethyl disulfide to afford methyl 2,3-xylyl sulfide in 96% yield. The compound was oxidated with hydrogen peroxide in acetic acid to form the corresponding racemic sulfoxide in 94% yield: mp71.2 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 7.82 (d, 1H,, $J = 7.8$ Hz), 7.37 (t, 1H,, $J = 7.8$ Hz), 7.29 (d, 1H, $J = 7.6$ Hz), 2.66 (s, 3H), 2.31 (s, 3H), 2.26 (s, 3H), IR (KBr) 2996, 1560, 1459, 1049, 804, 680 cm^{-1}. Anal. Calcd for $C_9H_{12}OS$: C, 64.24; H, 7.19. Found: C, 64.32; H, 7.29.

Preparation of Inclusion Compounds of Alkyl Phenyl Sulfoxide and the Dipeptides. After dipeptide (0.15 mmol) and a racemic sulfoxide (**1**, **2**, or **3**) (0.30 mmol) were dissolved in methanol (2 mL), the resulting mixture was allowed to stand at an ambient temperature for several days. In the case of (*S*,*S*)-Ala-Phg, (*S*,*S*)-Ala-Phg (0.15 mmol) was previously dissolved in small amount of water. The deposited inclusion compound was collected by filtration and washed with water and $CHCl_3$

Determination of G/H Ratio, Stereochemistry, and Enantiomeric Excess in the Inclusion. G/H ratio means the ratio of the sulfoxide (guest) to the dipeptide (host) in the inclusion compound. After dissolving the sample with d_4-MeOH, the ratios were determined by ^1H NMR measurement. In the case of (*S*,*S*)-Ala-Phg, a drop of DCl/D_2O was added for complete solution in the NMR sample tube. The included sulfoxide was isolated by dissolution of the inclusion compound in 0.1 M aqueous HCl (4 mL) and extraction with $CHCl_3$. Absolute stereochemistry of recognized sulfoxides was determined by a chiral shift reagent [(*R*)-(+)-2,2′-dihydroxy-1,1′-binaphthyl ((*R*)-BINOL, 1 mol equiv for the sulfoxide)].[16] Enantiomeric excess of the sulfoxide was determined by a chiral HPLC (Daicel Chiralcel OB-H). Analytical conditions and properties of all sulfoxides except for methyl 2,3-xylyl sulfoxide **3d** have already reported in our previous literature.[5a] Only the enantiomeric excess of methyl 2,5-xylyl sulfoxide **3e** was determined by optical rotation, because the HPLC peaks of enantiomers were overlapped.

Methyl 2,3-Xylyl Sulfoxide 3d. $[\alpha]^{25}_D = -229.1$ (*c* 0.1 $CHCl_3$ 92% ee *S*), HPLC eluent, hexane/2-propanol (4:1), flow rate = 0.4 mL/min, t_R (*S*) = 23.1 min, t_R (*R*) = 35.3 min); ^1H NMR (with (*R*)-BINOL in $CDCl_3$) δ 2.25 (s, 3H), 2.33 (s, 3H), 2.63 (s, 0.09H, *R* minor), 2.65 (s, 2.91H, *S* major), 7.13−7.39 (m, 3H).

Methyl 2,5-Xylyl Sulfoxide 3e. $[\alpha]^{25}_D = -87.4$ (*c* 0.285, acetone 72% ee *S*).[5a]

Crystallographic Data for the Inclusion Compounds. A methanol solution of the dipeptide and the guest (**1**, **3h**, or **2b**) was prepared in a vial, and then a lid of the vial was loosely closed for evaporation of the solvent. The samples were allowed to stand for several days to form the desirable single crystals. Data collection was performed on a Bruker APEXII CCD diffractometer with graphite-monochromated Mo *K*α ($\lambda = 0.71073$) radiation. The structures were solved by a direct method SHELXS-97[17] and refined by SHELXL-97[17] in a computer program package from Bruker AXS. Hydrogen atoms are calculated in appropriate position.

Inclusion Compound of (*S*,*S*)-Ile-Phg with Methyl Phenyl Sulfoxide [(*S*,*S*)-Ile-Phg·1]. Colorless crystals; dec 168.2 °C; $C_{21}H_{28}N_2O_4S$ MW 404.51, crystal dimensions 0.42 × 0.05 × 0.03 mm, orthorhombic $P2_12_12_1$ $a = 5.683(2)$ Å, $b = 16.352(6)$ Å, $c = 22.299(9)$ Å, $V = 2072.3(14)$ Å^3, $Z = 4$, $T = 173$ K, $d_{calcd} = 1.297$ g cm^{-3}, 7004 reflections measured, 2337 independent, $R = 0.0464$ (1848 reflections with $I > 2.00\sigma(I)$), w$R2 = 0.0920$, $S = 1.052$, 258 parameters, residual electron density 0.047/−0.26. IR (KBr) 3381, 2964, 2549, 2098, 1674, 1597, 1496, 1362, 1016, 733, 690 cm^{-1}; powder X-ray diffraction (I/I_0) 13.1 (0.16), 11.1 (0.34), 9.2 (0.16), 6.8 (0.24), 5.3 (0.22), 4.9 (1.00), 4.7 (0.55), 4.0 (0.60), 3.7 (0.47), 3.6 (0.43), 3.5 (0.39), 2.8 Å (0.32). Anal. Calcd for $C_{14}H_{20}N_2O_3 \cdot 1.00(C_7H_8SO) \cdot 0.20H_2O$: C, 61.80; H, 7.01; N, 6.86. Found: C, 61.82; H, 7.06; N, 6.89.

Inclusion Compound of (*S*,*S*)-Leu-Phg with Methyl 3,4-Xylyl Sulfoxide [(*S*,*S*)-Leu-Phg·3h)]. Colorless crystals; dec 161.7 °C; $C_{23}H_{32}N_2O_4S$ MW 432.57, crystal dimensions 0.40 × 0.08 × 0.05 mm, orthorhombic $P2_12_12_1$ $a = 5.8273(10)$ Å, $b = 15.945(3)$ Å, $c = 24.097(4)$ Å, $V = 2239.0(7)$ Å^3, $Z = 4$, $T = 173$ K, $d_{calcd} = 1.283$ g cm^{-3}, 6387 reflections measured, 2008 independent, $R = 0.0546$ (1823 reflections with $I > 2.00\sigma(I)$); w$R2 = 0.0992$, $S = 1.046$, 278 parameters, with heavy atoms refined anisotropically, residual electron density 0.747/−0.363; IR (KBr) 3386, 2958, 2117, 1676, 1583, 1496, 1375, 1018, 731, 696 cm^{-1}; powder X-ray diffraction (I/I_0) 13.3 (0.37), 12.1 (0.49), 11.5 (0.63), 9.6 (0.32),7.2 (0.41), 5.0 (0.77), 4.6 (1.00), 4.0 (0.84), 3.7 (0.81), 3.6 (0.69), 3.4 Å (0.46). Anal. Calcd for $C_{14}H_{20}N_2O_3 \cdot 0.96(C_9H_{12}OS) \cdot 0.10H_2O$: C, 63.59; H, 7.48; N, 6.55. Found: C, 63.52; H, 7.48; N, 6.75.

Inclusion Compound of (*S*,*S*)-Ile-Phg with Methyl 2-Tolyl Sulfoxide [(*S*,*S*)-Ile-Phg·2b]. Colorless crystals; dec 169.2 °C; $C_{22}H_{30}N_2O_4S$ MW 418.54, crystal dimensions 0.42 × 0.10 × 0.06 mm, orthorhombic $P2_12_12_1$ $a = 5.3975(5)$ Å, $b = 13.4459(11)$ Å, $c = 29.519(3)$ Å, $V = 2142.3(3)$ Å^3, $Z = 4$, $T = 173$ K, $d_{calcd} = 1.298$ g cm^{-3}, 11481 reflections measured, 4448 independent, $R = 0.0339$ (3960 reflections with $I > 2.00\sigma(I)$), w$R2 = 0.0698$, $S = 0.981$, 268 parameters., residual electron density 0.212/−0.220. IR (KBr) 3213, 3051, 2960, 2359, 1678, 1599, 1367, 1238, 1007, 731,696 cm^{-1}; powder X-ray diffraction (I/I_0) 14.7 (1.00), 10.1 (0.70), 8.0 (0.38), 5.6 (0.38), 5.6 (0.80), 5.1 (0.80), 4.5 (0.97), 4.2 (0.64), 4.0 (0.62), 3.7 (0.39), 3.5 (0.52), 3.3 (0.85), 3.0 (0.37). Anal. Calcd for $C_{14}H_{20}N_2O_3 \cdot 1.00(C_8H_{10}SO) \cdot 0.10H_2O$: C, 62.86; H, 7.24; N, 6.66. Found: C, 62.61; H, 7.27; N, 6.66.

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Supporting Information Available: Experimental methods, ^1H and ^{13}C NMR spectra for new compounds, and crystallographic data in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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